

Application For Research Grant

Date: March 29, 1955

1. Name of Investigator: Sheppard M. Walker
2. Title: Associate Professor of Physiology
3. Institution: University of Louisville School of Medicine
& Address: 101 West Chestnut Street, Louisville 2, Kentucky

4. Project or Subject: Effect of smoking and of blood levels ^{of} tobacco products on the heart.
- I. Acute experiments. A comparison of reflex action and of direct action of tobacco derivatives on the induction of ventricular extrasystoles in the dog and in the human.
- II. Chronic experiments and long range observations. Effect on cardiac response in the dog and in the human of prolonged treatment with tobacco derivatives.

5. Detailed Plan of Procedure (Use reverse side if additional space is needed): Acute experiments. For some time we have been looking for a reliable method for sensitization of the ventricles in the dog by stimulation of the cardiac sympathetic nerves. Now we have found that central sympathetic stimulation by that intracisternal injection of a mixture of mono- and dibasic potassium phosphate (0.03 cc./kg. of M/6 solution) does sensitize the ventricles to chloroform inhalation in vagotomized dogs previously anesthetized with sodium barbital. The chloroform under these conditions, produces ventricular extrasystoles. This method of sensitization by nerve stimulation has the advantage of being physiological, inasmuch as any trace of the potassium phosphate leaving the cerebrospinal fluid and entering the blood stream does so after the sympathetic stimulation is completed. Furthermore, we are able to induce the sensitization with sympathetic nerve stimulation alone, i.e., in vagotomized dogs. We plan to use this method of sensitization as a basis for comparative studies as follows: (1) Inhalation of tobacco smoke (previously collected in a Douglas bag) in one group of dogs. (2) Inhalation of filtered tobacco smoke in a second group of dogs. (3) Intravenous injection of tobacco derivatives, including nicotine and various irritants, in a third group of dogs. Similar comparative studies will be carried out in unsensitized dogs. In the human we plan to ~~also~~ observe the incidence of ventricular extrasystoles induced, by filtered and non-filtered smoking, in non-smokers and in inveterate smokers among the medical students before and after local anesthesia of the buccal cavity and the upper respiratory passages. Our rationale for these approaches to the problem of ventricular extrasystoles is based on the reports in the literature that smoking in man induces extrasystoles, while intravenous injection of nicotine in animals does not induce extrasystoles when the animal has previously been sensitized with agents like barium or chloroform.

1003537226

B. Chronic experiments and long range observations. We plan to house weanling puppies on the roof of the Medical School building and place a part of these puppies on diets containing various tobacco derivatives. During the course of development of these puppies we shall keep records of growth rates and food intakes for purposes of comparison with the litter mate controls. At regular intervals we shall obtain ECG recordings before and after stimulation with intracisternal potassium phosphate. The final experiment on these animals after they have reached maturity, will include observations on the effect of electrically induced ventricular tachycardia. Long range observations on the human will include ECG recordings, from non-smokers and smokers among medical students, taken annually and filed away for purposes of comparison over a period of years. The purpose of this study in man is to look for evidence of induction of cardiac damage within a single profession. Studies in the past on man have been primarily concerned with effects of smoking on the incidence of fatality in persons already showing cardiac damage, at the time the study was begun.

1003537227

6. Budget Plan:

Salaries	\$5,000.00
Expendable Supplies	2,000.00
Permanent Equipment	2,000.00
Overhead	820.00
Other - Travel	400.00
Total	\$10,220.00

7. Anticipated Duration of Work: Three years on studies with dogs. Many years on long range studies with man.

8. Facilities and Staff Available:

1. Facilities:
 - a. Grass EEG machine (4 channel)
 - b. Offner EEG machine (4 channel)
 - c. Kymograph for study of respiratory and blood pressure changes in the dog.
 - d. Douglas bags for inhalation studies in the dog.
 - e. Thyatron stimulator for electrical induction of tachycardia in the ventricles of the dog.
 - f. Sundry laboratory apparatus.

II. Staff: a. Sheppard M. Walker, b. animal caretaker to feed and weigh animals and

9. Additional Requirements: clean their living quarters, c. Drs. H. C. Lawson and J. P. Holt are available for consultation on interpretation of results.

- a. A research associate interested in our type of research and capable of helping me set up and carry out experiments. (I have in mind a man who has expressed interest in our research.)
- b. Dog cages and shelters on the roof of the Medical School building.
- c. Supplies of dogs and food.
- d. Supplies of EEG recording paper.
- e. Supplies of tobacco and tobacco derivatives.

10. Additional Information (Including relation of work to other projects and other sources of supply):

We are not aware of a current project that is related to the work we have proposed. We would like to state at this point what we believe to be the significance of our approach, as outlined in our proposed work. (A) We are studying, acutely, the combined effects of smoke inhalation and elevated sympathetic activity because we believe that irritative reflexes initiated in the mucous membrane of the buccal cavity and respiratory passages, together with central excitation associated with the act of smoking, are largely responsible for the extrasystoles observed in man. (B) In our long range studies designed to look for cardiac damage, the blood levels of tobacco derivatives in the puppies would be maintained at a considerably higher level than the levels of tobacco derivatives in the blood of inveterate smokers. If it should be shown that high blood levels of tobacco derivatives in dogs do not induce cardiac damage, then cardiac damage observed in inveterate smokers could not be attributed to blood levels of tobacco derivatives, without reservation.

Signature /s/ Sheppard M. Walker
Director of Project

Business Officer of the Institution

1003537228